REMARKS

Claims 1-3, 9-10, 14, 16-17, 21, 26, 30-31, 35, 40, 44-45, 49, 54, 58-59, 63, 68, 72-82, 84, 90-91, 93-94, 96-97, 99, 104, and 124-125 are pending in this application. Claims 79, 80, and 125 have been canceled. New claims 126-131 have been added. Claim 1 has been amended to replace the term "and" with the term "or". Claims 2-3, 9-10, 14, 16-17, 21, 26, 30-31, 35, 40, 44-45, 49, 54, 58-59, 63, 68, 72-78, 81, 84, 91, 94, 97, 104, and 124 have been amended to add the phrase "or a pharmaceutically acceptable salt, hydrate or solvate thereof". Claim 78 has been further amended to recite a method of agonizing a 5-$HT_{2c}$ receptor. Claim 81 has been further amended to recite a method of treatment of various disorders. Claim 82 has been amended to preserve antecedent basis from claim 81. Claims 91, 94, and 97 have been further amended to eliminate the multiple dependencies. Support for the amendments and new claims can be found throughout the original claims and specification, for example, in original claim 79, 80, 81, and 82. No new matter has been added. After entry of this amendment, claims 1-3, 9-10, 14, 16-17, 21, 26, 30-31, 35, 40, 44-45, 49, 54, 58-59, 63, 68, 72-78, 81-82, 84, 90-91, 93-94, 96-97, 99, 104, 124, and 126-131 will be pending in this application.

## I. Supplemental Information Disclosure Statement

Applicants will be filing a supplemental information disclosure statement within the next few days for consideration by the Examiner. Applicants thank the Examiner for her consideration of the previously submitted information disclosure statement.

## II. The Claims Are Enabled

### A. Solvates and Hydrates

Claims 1-3, 9, 10, 14, 16, 17, 21, 26, 30, 31, 35, 40, 44, 49, 54, 58, 59, 63, 68, 72-82, 84, 90, 91, 93, 94, 96, 97, 99, 104, 124, and 125 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office alleges that the specification "does not reasonably provide enablement for solvates or hydrates" (Office Action, page 2). Citing to *Morton International Inc. v. Cardinal Chemical Co.*, 28 U.S.P.Q.2d 1190

(Fed. Cir. 1993), the Offices states that "numerous examples presented all failed to produce a hydrate and a solvate" (Office Action, page 2). The Office further states that " applicants must show that hydrates and solvates can be made, or limit the claims accordingly" (Office Action, page 2).

Applicants respectfully disagree and assert that the solvates and hydrates of the claimed compounds are fully enabled. As will be recognized, the enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons of skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.
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> ... it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Thus, any assertion by the Patent Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974). Further, the proper standard for an enablement inquiry rests on whether one skilled in the art would be able to make and use the invention without undue

experimentation. *In re Wands*, 8 U.S.P.Q.2d at 1404. Factors for consideration in determining whether undue experimentation is necessary to make and use the invention include 1) the quantity of experimentation necessary; 2) the amount of direction or guidance presented; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims.

As a preliminary matter, the Office's citation of *Morton* is misplaced. In *Morton*, the claims were directed to organotin compounds having "partial connectivity". *Morton*, 28 U.S.P.Q.2d at 1193. Noting that "[e]ven with the aid of sophisticated analytical instrumentation and the use of model systems", there was no evidence that the claimed compounds with the required connectivity could even exist. *Id.* Further, there was no evidence the procedures in the specification or the defendant's process would produce compounds with the "partial connectivity". *Id.* at 1193-94. Applicants respectfully assert that the claimed solvates and hydrates present a far different situation from that in *Morton*. As summarized below, there is clear evidence that hydrates and solvates are quite common and can be formed by routine methods. Hence, there is no question that hydrates and solvates can exist, unlike the compounds having partial connectivity in *Morton*. Further, unlike the unsuccessful preparative routes in *Morton*, the Office has failed to point to any section of the specification which suggests that Applicants attempted and failed to produce a solvate or hydrate of the claimed compounds.

Further, despite the Office's insistence to the contrary, the enablement of the solvates and hydrates of the claimed compounds is not dependent on the presence of working examples. The Office insists that Applicants must "show that hydrates and solvates [of the claimed compounds] can be made, or limit the claims accordingly" (Office Action, page 2). With respect to lack of working examples, the courts have held that there is no requirement for a "working" example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski,* 164 U.S.P.Q. 642 (C.C.P.A. 1970); *Ex parte Nardi*, 229 U.S.P.Q. 79 (Pat. Off. Bd. App. 1986). As detailed below, Applicants respectfully assert that one skilled in the art could make the hydrates and solvates of the claimed compounds without undue experimentation.

As will be appreciated, the test for whether experimentation would be undue is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine. *Wands*, 8 U.S.P.Q.2d at 1404. In *Wands*, the Office had rejected the appealed claims, directed to methods for assaying HBsAg using high-affinity IgM monoclonal antibodies, as lacking enablement. *Id.* at 1402. The Office alleged that the production of high-affinity IgM anti-HBsAg antibodies was unpredictable and unreliable and, therefore, would require undue experimentation. *Id.* The Federal Circuit disagreed, finding that undue experimentation would not be required. *Id.* at 1406. Even though screening for hybridomas involved several, labor-intensive steps (see the steps in Table 1), the court found that this amount of effort was not excessive or undue, as the methods needed to practice the invention were well-known and the level of skill in the art was high. *Id.* The court noted that a finding of undue experimentation would not be required even if the success rate for producing the antibodies was only 2.8% as suggested by the Office (as contrasted with the 44% success rate advanced by the applicant). *Id.*

In stark contrast with the antibody-making procedures at issue in *Wands*, the preparation of hydrates and solvates of a particular organic molecule is a substantially easier and overwhelmingly simpler process, which requires significantly fewer steps and much less time than the preparation of a monoclonal antibody. Table 1 provides a step-by-step comparison of some of the major steps involved in the production of a monoclonal antibody (as disclosed in *Wands*) and the one step involved in making a hydrate or solvate. To make hydrates and solvates, samples of the organic compound are exposed to water or various different solvents.[1]

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[1] For example, Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids", in Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittain, vol. 95, chapter 5, Marcel Dekker, Inc., New York 1999, pages 183-226 (hereinafter "Guillory") at pages 202-205 and pages 205-208 describe the routine preparation of hydrates and solvates of compounds, respectively, as illustrated in the excerpts below:

> Simply exposing an anhydrous powder to high relative humidity can often lead to formation of a hydrate.

Guillory, page 204.

> Often, when solvents are employed in the purification of new drug substances by recrystallization, it is observed that the isolated crystals include solvent molecules...

Once the hydrates and solvates are formed, they can be readily analyzed by routine methods or other routine techniques to detect and quantify the presence of hydrate or solvate molecules in the sample. Exposure of the organic compounds to water and various solvents is conducted through simple and routine methods such as letting the samples sit open to air for set amounts of time, as well as slurrying and/or crystallizing the samples from water or solvent. In fact, it is difficult to conceive of a scientific method that is simpler to perform than placing a powder on a dish and letting it sit out on a humid day. Other typical procedures for making and identifying hydrates and solvates are described in Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids", in Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittain, vol. 95, chapter 5, Marcel Dekker, Inc., New York 1999, pages 183-226 (hereinafter "Guillory") (enclosed). Hence, screening for hydrates and solvates merely uses methods that are very well known in the art and considered quite simple.[2] As is clearly shown in Table 1 and summarized above, the production of a monoclonal antibody is much more complex and time-consuming than the production of a hydrate or solvate, yet the *Wands* court concluded that the production of a monoclonal antibody was not excessive and undue. Hence, it is clearly inconsistent to allege that the production of hydrates and solvates would require undue experimentation, while the production of monoclonal antibodies would not require undue experimentation.

Further, after searching the PTO database of issued patents in a cursory manner, the following U.S. Patents were readily identified as having claims including hydrates and/or solvates, yet having no enablement rejections to the same: U.S. Pat. Nos. 7232823, 7230024, 7229991, 7211591, 7173037, 7157466, and 7105523. Applicants see no difference between these patents and the present application with respect to enablement of hydrates and solvates and, thus, believe that the enablement rejection in this application should be withdrawn. For all of

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Guillory, page 205.

[2] In fact, there are numerous companies that routinely provide this screening service (usually combined with polymorph screens) and advertise how quickly and efficiently they can identify hydrates and solvates. Example companies offering these services include Wilmington PharmaTech (Wilmington, DE) and Avantium Technologies (Amsterdam).

these reasons, Applicants respectfully assert that all of the requirements of 35 U.S.C. § 112, first paragraph, have been met and request that the claim rejections be withdrawn.

**Table 1**

| Step | Monoclonal Antibody | Hydrate or Solvate |
|---|---|---|
| 1 | immunize animal | expose the compound to water or solvent |
| 2 | remove the spleen from the immunized animal | |
| 3 | separate the lymphocytes from the other spleen cells | |
| 4 | mix the lymphocytes with myeloma cells | |
| 5 | treat the mixture to cause fusion between the lymphocytes and the myeloma cells to make hybridomas that hopefully secrete the desired antibody | |
| 6 | separate the hybridoma cells from the unfused lymphocytes and myeloma cells by culturing in a medium in which only hybridoma cells survive | |
| 7 | culture single hybridoma cells (often 100 of different cells) in separate chambers | |
| 8 | assay the antibody secreted from each hybridoma culture to determine if it binds to the antigen | |

**B. Methods**

Claims 78-81, 84, 90, 91, 93, 94, 96, and 125 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. In particular, the Office alleges that the "terms 'disorders of the central nervous system, cardiovascular disorders and gastrointestinal disorders" covers a broad array of different disorders that have different modes of action and different origins" (Office Action, page 3). The Office goes on to list several central nervous system disorders including AD, Parkinson's disease, Pick's disease, ALS,

dementias, spinal muscular atrophies, spinocerebellar degenerations, retinitis pigmentosas, progressive ataxias, Huntington's disease, and Down's syndrome, stating that "the great majority of these have no treatment at all" (Office Action, pages 3-5). The Office further alleges that "prophylaxis...is not remotely enabled", as there is no "way of identifying those people who may develop a disorder of the central nervous system, cardiovascular disease, gastrointestinal disorders, etc." (Office Action, page 5). The Office concludes that "[w]here utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of *in vivo* efficacy by those skill in the art" (Office Action, pages 5-6).

As a preliminary matter, Applicants note that the Office appears to have acknowledged the enablement of the **methods of treatment and prophylaxis of obesity** (original claim 82, which are now amended claim 82 and new claim 127) and a **method of controlling weight gain** (original claims 97 and 99), as these claims are not included in the listing of the rejected claims in section 2 and 3 of the Office Action (pages 3-7).[3] Further, contrary to the requirements set forth by the court in *In re Marzocchi*, the Office has not provided any specific evidence demonstrating why the remaining methods could not be used without undue experimentation. Instead, the Office has simply made unsupported statements regarding the allegedly speculative efficacy of the claimed methods. While Applicants disagree with the Office's conclusions regarding the enablement of the claimed methods, Applicants have canceled claim 79-80 and 125, solely to advance prosecution. Applicants have further amended claims 78 and 81 and added new claims 126-131. Applicants reserve the right to pursue the canceled subject matter in a future continuing application. Applicants respectfully assert that the methods of the amended and new claims are fully enabled for the reasons set forth below.

### i. Methods of agonizing the 5-$HT_{2c}$ receptor

[3] The Office has instead rejected original claims 82, 97, and 99 solely with regard the enablement of the terms "solvate" and "hydrate" (see section 1, page 2 of the Office Action). Applicants have addressed these rejections in section II.A of this response.

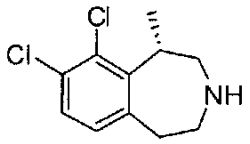
Claims 78, 79, and 125 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. As noted above, claims 79 and 125 have been canceled, solely to advance prosecution. Further, claim 78 has been amended to recite a methods of agonizing the 5-$HT_{2c}$ receptor. Applicants respectfully assert that amended claim 78 is fully enabled. Compounds of claim 1 have been shown to be agonists of the 5-$HT_{2c}$ receptor in an IP accumulation assay (see specification, Example 1, Table 1). This conclusion is substantiated by the $EC_{50}$ data for compounds 7n, 7o, 7x, 7y, 7z, 7aa, 7bb, and 7cc in Smith et al., "Discovery and structure-activity relationship of (1R)-8-chloro-2,3,4,5-tetrahydro-1-methyl-1H-3-benzazepine (lorcaserin), a selective serontonin 5-$HT_{2c}$ receptor agonist for the treatment of obesity", *Journal of Medicinal Chemistry*, (2008), 51:305-313 (hereinafter "Smith"). Accordingly, Applicants respectfully assert that the methods of amended claim 78 is fully enabled and requests that the claim rejection be withdrawn.

**ii. Methods of decreasing food intake (claim 91 and 93) and inducing satiety (claim 94 and 96)**

The Office rejects claims 91, 93, 94, and 96, reciting methods of decreasing food intake and inducing satiety, but fails to give any reason for why these methods are not enabled. Indeed, in its discussion of the enablement rejection, the Office Action is silent with regard to methods of decreasing food intake and inducing satiety. Hence, Applicants respectfully assert that the Office has failed to carry its burden under *In re Marzocchi* to provide evidence or reasoning to back up its assertions of non-enablement. Accordingly, the burden has not shifted to Applicants to provide rebuttal evidence to show the enablement of the claimed methods.

Nonetheless, Applicants respectfully note that the art clearly demonstrates that one skilled in the art would accept that a 5-$HT_{2c}$ agonist can decrease food intake and induce satiety, without having to engage in undue experimentation. For example, 5-$HT_{2c}$ agonists have been shown to increase satiety and induce undereating, while 5-$HT_{2c}$ knock-out mice have been shown to be hyperphagic and unresponsive to the anorectic effects of 5-$HT_{2c}$ agonists (see e.g., Bickerdike, "5-$HT_{2c}$ receptor agonists as potential drugs for the treatment of obesity", *Current*

*Topics in Medicinal Chemistry*, 3:885-897 (2003); and Tecott, et al., "Eating disorder and epilepsy in mice lacking 5-$HT_{2c}$ serotonin receptors", *Nature*, 374:542-546 (1996)). Hence, one skill in the art would accept that 5-$HT_{2c}$ agonists, such as the compounds of claim 1, would be useful to decrease food intake and induce satiety as recited by the claimed methods without engaging in undue experimentation. This conclusion is substantiated by the data for compound 7z in Smith, page 308, Table 2, showing a dose-dependent reduction in acute food intake in studies in rats. Accordingly, Applicants respectfully assert that the methods of claims 91, 93, 94, and 96 are fully enabled and request that the claim rejections be withdrawn.




Compound 7z

**iii. Methods of treating depression, atypical depression, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sexual dysfunction, psychoses, schizophrenia, and epilepsy (amended claims 81, 84, and 90 and new claims 128-131)**

As a preliminary matter, Applicants have amended independent claim 81 to recite particular disorders. The Office fails to provide any reason for why the particular treatment methods of independent claim 81, and dependent claims 84 and 90, are not enabled.[4] While the Office Action briefly mentions epilepsy in a laundry list of central nervous system disorders, the Office fails to give any specific reason for the alleged lack of enablement of this particular disorder. Further, in its discussion of the enablement rejection, the Office Action is completely silent to the remaining disorders in amended claim 81. Hence, Applicants respectfully assert that the Office has failed to carry its burden under *In re Marzocchi* to provide evidence or reasoning to back up its assertions of non-enablement. Accordingly, the burden has not shifted to Applicants to provide rebuttal evidence to show the enablement of the claimed methods.

[4] Later in the Office Action, the Office separately rejected methods of treating drug and alcohol addition. We address that rejection in section II.B.v below.

Nonetheless, Applicants respectfully note that the art clearly demonstrates that one skilled in the art would accept that a 5-$HT_{2c}$ agonist can treat the disorders recited by amended claim 81, without having to engage in undue experimentation. *See e.g.,* Tecott, et al., "Eating Disorder and Epilepsy in Mice Lacking 5-$HT_{2c}$ Serotonin Receptors", *Nature*, 374:542-546 (1996) (epilepsy-5-$HT_{2c}$ knock-out mice subject to death from seizures); Isaac, "The 5-$HT_{2C}$ receptor as a potential therapeutic target for the design of antiobesity and antiepileptic drugs" *Drugs of the Future* (2001), 26(4), 383-393 (epilepsy); Jenck, et al., "Antiaversive effects of $HT_{2c}$ receptor agonists and fluoxetine in a model of panic-like anxiety in rats", *European Neuropsychopharmacology*, 8:161-168 (1998) (social phobias, panic disorders); Millan, et al., "$HT_{2c}$ Receptors Mediate Penile Erections in Rats: Actions of Novel and Selective Agonists and Antagonists", *Eur. J. Pharmacol.* 325:9-12 (1997) (sexual dysfunction); Martin et al. "5-$HT_{2C}$ receptor agonists pharmacological characteristics and therapeutic potential", *Journal of Pharmacology and Experimental Therapeutics* (1998), 286(2), 913-924 (sexual dysfunction-eliction of penile erections, obsessive-compulsive disorder-reduction in compulsive burying and schedule-inducted polydipsia in rats and compulsive scratching in squirrel monkeys); Bos et al., "Novel Agonists of 5$HT_{2C}$ Receptors. Synthesis and Biological Evaluation of Substituted 2-{Indol-l-yl)-l-methylethylamines and 2-(Indeno[1,2-b]pyrrol-l-yl)-1-methylethylamines. Improved Therapeutics for Obsessive Compulsive Disorder, *Journal of Medicinal Chemistry* (1997), 40(17), 2762-2769 (obsessive-compulsive disorder-reduction in schedule-induced polydipsia in rats); Chahal, *ThomsonPharma, Literature and News Report*, May 17-18, 2000 (depression); Piesla et al., "Atypical Antipsychotic-like Effects of 5-$HT_{2c}$ Agonists", *Abstracts of the 8th International Congress on Schizophrenia Research. British Columbia*, Canada, (April 28-May 2, 2001), Schizophrenia Research 49:95 (col. 2) (psychoses, schizophrenia); Clinical trial NCT00768612, "Study Evaluating Safety and Tolerability of Vabicaserin in Patients With Sudden Worsening of Schizophrenia Study", *http://clinicaltrials.gov/ct2/show/record /NCT00768612* (planned clinical trial for vabicaserin, 5-$HT_{2C}$ agonist, for schizophrenia); and Rosenzweig-Lipson, et al., "Vabicaserin: effects of a novel 5HT2C agonist on medial prefrontal cortex neurotransmission, cognition and sensorimotor gating", *20th ECNP Congress*, Vienna,

Austria (2007) (psychoses, schizophrenia). Accordingly, Applicants respectfully assert that the methods of claims 81, 84, 90, and 126 are fully enabled and request that the claim rejections be withdrawn.

**iv. Methods of preventing depression, anxiety, psychoses, schizophrenia, and cardiovascular disorders (new claim 126)**

The Office alleges that the prophylaxis of the disorders recited in original claims 80-81, 84, and 90 are not non-enabled. In particular, the Office states that "[i]nstant claim language embraces disorders not only for treatment but also for prophylaxis, which is not remotely enabled" (Office Action, page 5). The Office further alleges that there is "no evidence of record, which would enable the skilled artisan in the identification of people who have the potential of becoming afflicted with the disorders claim herein" (Office Action, page 5). While Applicants disagree with the Office's assertion, the term "prophylaxis" has been deleted from original claim 81. New claim 127 has been added to recite methods of prophylaxis of obesity, depression, anxiety disorders, psychoses, schizophrenia, and cardiovascular disorders.[5]

First, the Office appears to distinguish between methods of treatment and prophylaxis, seemingly implying that methods of prophylaxis are subject to a higher standard for enablement. In a non-precedential decision, the Board of Patent Appeals and Interferences rejected this type of distinction. *Ex parte Sung Y. Cho*, Appeal No. 2001-2646, Application No. 08/463,951 (Bd. Pat. App. & Inter. 2001) (attached for the Office's convenience). In *Cho*, the Office had indicated that methods of treating pain, asthma, and inflammation were enabled, but alleged that methods of preventing these disorders were not enabled. *Cho*, Appeal No. 2001-2646, at page 7. The Board held that the Office had failed to carry its burden to show non-enablement of the methods of preventing the disorders reasoning that:

> Logically, if the recited compounds are useful for treating conditions such as pain and inflammation once they exist, they would also be expected to be effective in preventing pain or inflammation, if they were administered before the onset of pain or inflammation. The examiner has provided no reasoning to support a contrary conclusion.

[5] As noted above, the Office does not appear to contest the enablement of methods of prophylaxis of obesity.

Hence, it is improper for the Office to imply that methods of prophylaxis are somehow less enabled than methods of treatment, without providing evidence supporting its conclusion.

Moreover, the amended claims are fully enabled with regard to the identification of people who may develop depression, anxiety disorders, psychoses, and schizophrenia. For example, physicians can readily identify patients who have suffered from the disorder in the past and may use prophylactic therapy to prevent future episodes after the initial treatment period. *See e.g.*, Lam RW, Levitt AJ (1999) (eds), "Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder", Clinical & Academic Publishing, Vancouver, BC, Canada (e.g., page 13, recommending year-round prophylactic therapy for certain identifiable patients with seasonal depressive disorder); Wisner et al., "Postpartum Depression", *N. Engl. J. Med.*, (2002) 347(3): 194-199 (see, e.g., page 198, col. 1, recommending post-delivery prophylactic treatment for women who have a history of postpartum depression); Karasu et al., *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*, "Work Group on Major Depressive Disorder", 2nd Ed., pages 1-78 (2000) (see, e.g., page 25, section D, discussing the use of prophylactic treatment in patients who have had a major depressive episode); Barnes, "Pharmacological Strategies for Relapse Prevention in Schizophrenia", *Psychiatry*, (2004), 3(10): 37-40 (use of prophylactic antipsychotic treatment in schizophrenic patients). Further, risk factors for anxiety and depression in the elderly are reviewed in Vink et al., "Risk Factors for Anxiety and Depression in the Elderly: A Review", *J. Affect. Disord.*, (2007), doc. 101016/j.jad.2007.06.005. Niendam discusses studies of individuals identified at ultra-high risk for psychosis (Niendam et al., "Neurocognitive Performance and Functional Disability in the Pyschosis Prodrome", *Schizophrenia Research*, (2006), 84: 100-111). Similarly, criteria for identification of schizotaxia (pre-schizophrenia) are described in Tsuang et al., "Towards the Prevention of Schizophrenia", *Biol. Psychiatry*, (2000), 48: 349-356. Accordingly, Applicants respectfully assert that one of skill in the art would b to identify those who have the potential of becoming afflicted with the disorders recited by claim 126.

Further, since a higher risk of cardiovascular disorders, such as thrombosis and coronary artery disease, has been linked to obesity, one of skill in the art would expect that treatment of obesity through the use of 5-$HT_{2c}$ agonists, such as the compounds of the present invention, would protect against the development of cardiovascular disease. *See e.g.,* Garrison, "Defining obesity: An adventure in cardiovascular disease epidemiology", *Journal of Nutritional Biochemistry* (1998), 9(9), 493-500; Winkler, "Obesity and hemostasis", *Archives of Gynecology and Obstetrics* (1997), 261(1), 25-29; and Klein, "Outcome Success in Obesity", Obesity Research, (2001), 9(suppl. 4):354S-358S. Accordingly, Applicants respectfully assert that methods of prophylaxis of cardiovascular disorders are similarly enabled.

For all of these reasons, Applicants respectfully submit that the methods of prophylaxis are enabled and request that the claim rejections be withdrawn.

**v. Methods of treating drug and alcohol dependence (amended claim 81)**

Claims 78-81 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement with respect to "diagnosis, treatment, prevention, or alleviation...drug and alcohol addiction" (Office Action, page 6). The Office alleges that there "is not, and probably never will be a pharmacological treatment for 'drug addiction' generally" (Office Action, page 6). The Office asserts that alcohol and various drug addictions arise from involvement of different receptors and that, therefore, "[a]ll attempts to find a pharmaceutical to treat chemical addictions generally have thus failed" (Office Action, pages 6 and 7).

Applicants respectfully assert that these conclusory statements do not carry the Office's burden to provide evidence or reasoning to back up its assertions of non-enablement as required by *In re Marzocchi*. The Office has cited no evidence of the supposed complete lack of treatments available for chemical addictions. Indeed, the record before the Office clearly shows that 5-$HT_{2c}$ agonists have been shown to reduce cocaine, nicotine, and alcohol self-administration in animal studies (see e.g., Higgins, et al. "Serontonin and drug reward: focus on 5-$HT_{2c}$ receptors", *European J. of Pharmacology*, (2003), 480:151-162, at page 155-156).

Accordingly, Applicants respectfully assert that methods of treating drug and alcohol addiction are fully enabled and request that the claim rejections be withdrawn.

### III. The Claims Are Definite

Claims 78, 79, and 125 rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. The Office states that the "claim does not set forth any steps involved in determining which are the disorders capable of being treated by modulating the activity of the 5-$HT_{2c}$ receptor" (Office Action, page 7). The Office further alleges that "[d]etermining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation" and lists five criteria to "[k]eep in mind" (Office Action, page 7). First, the Office asks the question "[w]hat success rate is required to conclude our drug is a treatment", noting that no pharmaceutical is 100% successful (Office Action, pages 7-8). Second, the Office remarks that it is "quite common for pharmaceuticals to work or be safe at one dosage, but not at another that is significantly higher or lower" and asks "how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?" (Office Action, page 8). Third, the Office alleges that "[i]t may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease" and asks "how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?" (Office Action, page 8). Fourth, the Office asks "if the disease responds to our second drug but not the first, both of which are inhibitors *in vitro*, can one really conclude that the disease falls within the claim?" (Office Action, pages 8-9). Fifth, the Office alleges "[s]uppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug" (Office Action, page 9). The Office then concludes that "determining the scope of the claim will involve extensive and potentially inconclusive research" and that "[w]ithout it, one skill in the art cannot determine the scope of the claim" (Office Action, page 9).

As noted above, Applicants have canceled claims 79 and 125 and have amended claim 78 to recite a method of agonizing a 5-$HT_{2c}$ receptor. Applicants respectfully assert that amended claim 78 is definite. The Office has stated that the "claim does not set forth any steps involved in determining which are the disorders capable of being treated by modulating the activity of the 5-$HT_{2c}$ receptor" (Office Action, page 7). However, Applicants respectfully note that amended claim 78 does not recite a disorder "capable of being treated by modulating the activity of 5-$HT_{2c}$ receptor", but rather a method of agonizing the 5-$HT_{2c}$ receptor. Hence, the Office's concern regarding the scope of treatable disorders is irrelevant to claim 78.

Further, Applicants note that "undue experimentation" is the legal standard for enablement, not indefiniteness. Instead, claims are indefinite when, read in light of the specification, they do not reasonably apprise those skilled in the art of the scope of the invention. *Howmedia Osteonics v. Tranquil Prospects,* 401 F.3d 1367, 1371 (Fed. Cir. 2005). However, the claims must be so insolubly ambiguous that no narrowing construction can properly be adopted. *Bancorp v. Hartford Life*, 359 F.3d 1367, 1372 (Fed. Cir. 2004) (stating that when a claim "is not insolubly ambiguous, it is not invalid for indefiniteness").

While confusingly applying the incorrect legal standard in its analysis, the Office appears to be asserting that one of skill in the art could not determine the "true scope of the claim" (Office Action, page 9). As noted above, amended claim 78 recites a method of agonizing a 5-$HT_{2C}$ receptor using a compound of Formula (I). The scope of claim 78 is not insolubly ambiguous in nature, as the specification completely describes the compounds of Formula (I) and further delineates methods for determining whether a compound binds to and agonizes the 5-$HT_{2c}$ receptor (see specification at pages 46-47 (Example 1); see also, Smith et al., "Discovery and structure-activity relationship of (1R)-8-chloro-2,3,4,5-tetrahydro-1-methyl-1H-3-benzazepine (lorcaserin), a selective serontonin 5-$HT_{2c}$ receptor agonist for the treatment of obesity", *Journal of Medicinal Chemistry*, (2008), 51:305-313). Hence, one of skill in the art could readily determine the scope of amended claim 78. To the extent that the Office is alleging that amended claim 78 is non-enabled, Applicants refer the Office to section II.B.i of this response.

As to the Office's five points to "[k]eep in mind", Applicants respectfully note that these five points are merely open-ended speculative questions with absolutely no evidentiary support.[6] By contrast, Applicants have (1) shown that compounds of Formula (I) are agonists of the 5-$HT_{2c}$ (see previous paragraph); and (2) described the compounds of Formula (I) in detail (see claim 1 and specification). Applicants respectfully assert that one of skill in the art could clearly "interpret the metes and bounds of the claim so as to understand how to avoid infringement". M.P.E.P. § 2173.02. Accordingly, Applicants respectfully assert that claim 78 is definite and request that the claim rejection be withdrawn.

## IV. Claim Objections

Claims 90 and 125 are objected to under 37 C.F.R. § 1.75(c) as being in improper form because a multiple dependent claim must refer to multiple claims in the alternative (citing to M.P.E.P. § 608.01(n)). As noted above claim 125 has been canceled. Further, Applicants note that claim 90 is already in a proper form as it recites "The method according to claim 82 or 84..." Hence, claim 90 clearly refers to either claim 82 or 84 in the alternative. Indeed, it matches one of the acceptable multiple dependent wordings summarized in M.P.E.P. § 608.01(n):

### A. Acceptable Multiple Dependent Claim Wording

Claim 4. A gadget as in claim 2 or 3, further comprising ---

Accordingly, Applicants respectfully request that the claim objection be withdrawn.

## V. Conclusion

Applicants respectfully assert that rejections and objections of record have been overcome by way of this response. Allowance of all claims is respectfully requested. The Examiner is urged to contact Applicant's undersigned representative at (302) 778-8411 if there are any questions regarding the claimed invention.

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[6] To the extent that the Office's five points are related to enablement, Applicants respectfully assert that the non-supported, speculative nature of these questions fall far short of meeting the Office's burden under *In re Marzocchi*. Applicants refer the Office to section II of this response regarding the enablement of the pending claims.

The Commissioner is hereby authorized to debit any fee due or credit any overpayment to Deposit Account No. 06-1050. Further, if not accompanied by an independent petition, this paper constitutes a Petition for an Extension of Time for an amount of time sufficient to extend the deadline if necessary and authorizes the Commissioner to debit the petition fee and any other fees or credit any overpayment to Deposit Account No. 06-1050.

Respectfully submitted,

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*Ex parte Sung Y. Cho*

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